Upregulation of Vitamin C Transporter Functional Expression in 5xFAD Mouse Intestine.

Journal: Nutrients

Publication Year: 2021

Authors: Trevor Teafatiller, Christopher W Heskett, Anshu Agrawal, Jonathan S Marchant, Janet E Baulch, Munjal M Acharya, Veedamali S Subramanian

PubMed link: 33672967

Funding Grants: An exosome-based translational strategy to mitigate Alzheimer's disease neuropathology

Public Summary:
The process of obtaining ascorbic acid (AA) via intestinal absorption and blood circulation is carrier-mediated utilizing the AA transporters SVCT1 and SVCT2, which are expressed in the intestine and brain (SVCT2 in abundance). AA concentration is decreased in Alzheimer's disease (AD), but information regarding the status of intestinal AA uptake in the AD is still lacking. We aimed here to understand how AA homeostasis is modulated in a transgenic mouse model (5xFAD) of AD. AA levels in serum from 5xFAD mice were markedly lower than controls. Expression of oxidative stress response genes (glutathione peroxidase 1 (GPX1) and superoxide dismutase 1 (SOD1)) were significantly increased in AD mice jejunum, and this increase was mitigated by AA supplementation. Uptake of AA in the jejunum was upregulated. This increased AA transport was caused by a marked increase in SVCT1 and SVCT2 protein, mRNA, and heterogeneous nuclear RNA (hnRNA) expression. A significant increase in the expression of HNF1α and specific protein 1 (Sp1), which drive SLC23A1 and SLC23A2 promoter activity, respectively, was observed. Expression of hSVCT interacting proteins GRHPR and CLSTN3 were also increased. SVCT2 protein and mRNA expression in the hippocampus of 5xFAD mice was not altered. Together, these investigations reveal adaptive up-regulation of intestinal AA uptake in the 5xFAD mouse model.

Scientific Abstract:
The process of obtaining ascorbic acid (AA) via intestinal absorption and blood circulation is carrier-mediated utilizing the AA transporters SVCT1 and SVCT2, which are expressed in the intestine and brain (SVCT2 in abundance). AA concentration is decreased in Alzheimer's disease (AD), but information regarding the status of intestinal AA uptake in the AD is still lacking. We aimed here to understand how AA homeostasis is modulated in a transgenic mouse model (5xFAD) of AD. AA levels in serum from 5xFAD mice were markedly lower than controls. Expression of oxidative stress response genes (glutathione peroxidase 1 (GPX1) and superoxide dismutase 1 (SOD1)) were significantly increased in AD mice jejunum, and this increase was mitigated by AA supplementation. Uptake of AA in the jejunum was upregulated. This increased AA transport was caused by a marked increase in SVCT1 and SVCT2 protein, mRNA, and heterogeneous nuclear RNA (hnRNA) expression. A significant increase in the expression of HNF1alpha and specific protein 1 (Sp1), which drive SLC23A1 and SLC23A2 promoter activity, respectively, was observed. Expression of hSVCT interacting proteins GRHPR and CLSTN3 were also increased. SVCT2 protein and mRNA expression in the hippocampus of 5xFAD mice was not altered. Together, these investigations reveal adaptive up-regulation of intestinal AA uptake in the 5xFAD mouse model.